REMARKS

Applicants have amended their claims in order to further clarify the definition of various aspects of the present invention. Specifically, Applicants have amended claim 1 to recite a step of esterifying a reaction mixture of a racemic chromancarboxylic acid in an organic solvent comprising an alcohol and with a water content of at most 0.5% by weight, in the presence of an immobilized lipase which is derived from microorganisms belonging to the genus *Candida*. Claim 1 has been further amended to incorporate therein the subject matter of claim 9 as the chromancarboxylic acid, and to recite that a concentration of the alcohol in the organic solvent is from 1 to 10% by weight, and that the esterifying forms an ester of an enantiomer of the racemic chromancarboxylic acid, with this ester being the optically active chromancarboxylate. In connection with amendments to claim 1, note previously considered claims 4 and 9; see also the paragraph bridging pages 8 and 9, as well as the first full paragraph on page 8, of Applicants' specification. Claims 2 - 5, 8 and 9 have been canceled without prejudice or disclaimer, in light of amendments to claim 1; and dependencies of claims 6 and 10 have been amended in light of cancelling of claims 5 and 9. Claim 7 has been amended to be dependent upon claim 1.

Applicants have amended claim 11 to recite that, after the step of esterifying, a mirror image, of the chromancarboxylic acid which has been converted into the optically active carboxylic, remains, with the method further comprising a step of separating this mirror image from a reaction production solution after the esterification.

In addition, Applicants are adding new claims 13-19 to the application. Claims 13 and 14, each dependent on claim 1, respectively recites that only one enantiomer of the racemic chromancarboxylic acid is esterified in the step of

esterifying, and recites that the immobilized lipase is a biocatalyst which is capable of enantiospecifically esterifying only one enantiomer of the racemic chromancarboxylic acid in the organic solvent comprising the alcohol. Note, for example, the paragraph bridging pages 3 and 4 of Applicants' specification. Claim 15, dependent on claim 11, recites that the step of separating the mirror image of the chromancarboxylic acid which has been converted into the optically active chromancarboxylate includes adding sodium carbonate to remaining chromancarboxylic acid, after the step of esterifying, to form a sodium salt of the remaining chromancarboxylic acid, with the sodium salt being transferred into an aqueous layer. Note, for example, page 9, lines 14-22, of Applicants' specification. Claim 16, dependent on claim 1, recites that during the step of esterifying, water is removed such that the water content is at most 0.5% by weight. Note, for example, the paragraph bridging pages 8 and 9 of Applicants' specification. Claims 17-19 respectively expressly set forth subject matter expressly recited in claims 10-12, but are dependent respectively on claims 7, 17 and 18.

The contention by the Examiner with respect to the "listing of references in the Search Report", set forth in the paragraph bridging pages 2 and 3 of the Office Action mailed June 25, 2008, is noted. The Examiner is respectfully requested to indicate the "Search Report" referred to in this paragraph bridging pages 2 and 3 of the Office Action mailed June 25, 2008. In this regard, note that the Examiner has indicated consideration of the Supplementary European Search Report dated November 30, 2007, and submitted with the Information Disclosure Statement filed February 28, 2008, as well as the reference cited therein. Note the initialed copy of the Information Disclosure Statement dated February 28, 2008, enclosed with the Office Action mailed June 25, 2008. Thus, the Examiner is respectfully requested to indicate the "Search Report" referred to in the paragraph bridging pages 2 and 3 of

the Office Action mailed June 25, 2008, so that Applicants can properly respond to the contention by the Examiner that the references cited have not been considered. In this regard, note that the only reference cited in the aforementioned Supplementary European Search Report submitted with the Information Disclosure Statement filed February 28, 2008, is WO96/40975, which the Examiner has indicated has been considered by initialing the "Information Disclosure Statement By Applicant" dated February 28, 2008, and enclosed with the aforementioned Office Action mailed June 25, 2008.

Applicants respectfully traverse the rejection of their claims under the second paragraph of 35 USC 112, as being indefinite, particularly insofar as applicable to the claims as present amended. Thus, the Examiner contends that the claims are indefinite apparently because the preamble of the independent claim "states that it is a method for producing an optically active chromancarboxylate; however, no production of an optically active ester is in the body of the claim". Claim 1, as presently amended, recites the step of esterifying a racemic chromancarboxylic acid in an organic solvent comprising an alcohol "to form an ester of an enantiomer of the racemic chromancarboxylic acid, this ester being the optically active chromancarboxylate". Thus, it is respectfully submitted that claim 1 as presently amended recites production of the optically active chromancarboxylate, such that the basis for the rejection under the second paragraph of 35 USC 112, set forth in the second full paragraph on page 3 of the Office Action mailed June 25, 2008 is moot.

Applicants respectfully traverse the conclusion by the Examiner that claim 11 "is not interpretable", especially insofar as applicable to claim 11 as presently amended. Claim 11 as presently amended recites that a mirror image, of the chromancarboxylic acid which has been converted into the optically active chromancarboxylic, is separated from a reaction production solution after the

esterification. Thus, it is respectfully submitted that claim 11 is clear that it is the remaining acid (that is, the acid remaining after the ester of an enantiomer of the racemic chromancarboxylic acid has been formed) that is separated from a reaction production solution after the esterification, in claim 11. In connection therewith, note for example, page 9, lines 14-22 of Applicants' specification. Clearly, as presently amended, claim 11 recites that it is the acid remaining after forming the ester, which is separated in this claim 11.

The contention by the Examiner in connection with claim 11, that there is no antecedent basis for the recitation of the "optically active chromancarboxylate", is respectfully traversed. The Examiner's attention is respectfully directed to claim 1, upon which claim 11 is dependent, which recites a method for producing an optically active chromancarboxylate. Clearly, there is antecedent basis for "the optically active chromancarboxylate".

Similarly, Applicants respectfully traverse the contention by the Examiner that claim 12 lacks antecedent basis for the recitation of "the optically active chromancarboxylate". Claim 12 is dependent on claim 1, which recites "an optically active chromancarboxylate", providing antecedent basis for recitation thereof in claim 12.

The additional basis set forth by the Examiner for rejection of claim 12 as being indefinite, i.e., that the step would result in the reversal of the enantiomeric esterification, i.e., the racemic substrate of Formula (1) would result without the separation of the acid and ester prior to hydrolysis", is noted. Note, however, that according to the present method, the formed optically active carboxylate, e.g., remains in the organic layer, and can be isolated therefrom by distilling off the organic solvent under reduced pressure. As indicated previously in connection with claim 11, remaining non-reacted chromancarboxylic acid can be transferred into an

aqueous layer by the addition of sodium carbonate, separating the formed optically active chromancarboxylate from remaining non-reacted chromancarboxylic acid. As stated in the last full paragraph on page 9 of Applicants' specification, and to be illustrative and not limiting, after isolating the optically active chromancarboxylate from the organic layer, the isolated optically active chromancarboxylate "may be purified by recrystallization, etc., so as to attain desired chemical purity and optical purity". Thus, it is respectfully submitted that Applicants' disclosure as a whole teaches separation of the acid and ester; and, in particular, describes the step of hydrolyzing the optically active chromancarboxylate as recited in claim 12. It is respectfully submitted that nothing further is required for providing a method satisfying requirements of the second paragraph of 35 USC 112, i.e., defining metes and bounds of the present invention such that one of ordinary skill in the art would know whether any specific process practiced fell within or outside the scope of the present claims.

Applicants respectfully traverse the additional contention by the Examiner in connection with claim 12, that the step "does not further limit the stated intent of the method in the preamble which is a method of producing an optically active chromancarboxylate". It must be emphasized that the method recited in claim 1 is a method of producing an optically active chromancarboxylate. It is respectfully submitted that such method is clearly provided by the step of esterifying as in claim 1. It must be emphasized that the method is a method of producing the optically active chromancarboxylate, and does not recite a method of recovery or separation thereof.

The rejection of claims 1-12 under the second paragraph of 35 USC 112, as being incomplete for omitting essential steps, the Examiner contending that the omitted steps are "recovery or separation of the optically active

chromancarboxylate", is respectfully traversed. Again, it is emphasized that the present claims recite a method of producing an optically active chromancarboxylate; it is respectfully submitted that the Examiner has not established that this method of producing requires "recovery or separation" of the optically active chromancarboxylate, as essential steps of the producing method.

The additional contention by the Examiner in the second paragraph on page 4 of the Office Action mailed June 25, 2008 that the "metes and bounds of the claimed process are ... not clearly established or delineated" as it "would be expected from conventional preparation processes that the product must be isolated from the acid", is noted. However, it is again emphasized that the claims recite a method of producing; and it is respectfully submitted that consistent therewith, Applicants define processing which performs such "producing".

Applicants respectfully submit that all of the claims presented for consideration by the Examiner patentably distinguish over the teachings of the references applied by the Examiner in rejecting claims in the Office Action mailed June 25, 2008, that is, the teaching of Japanese Patent Document No. 2003-144190 and the publication by Kircher, et al., "Resolution of Racemic Mixtures via Lipase Catalysis in Organic Solvents", in J. Am. Chem. Soc., 1985, 107, 7072-7076, under the provisions of 35 USC 103.

It is respectfully submitted that the teachings of these applied references would have neither disclosed nor would have suggested such a method for producing an optically active chromancarboxylate as in the present claims, including the step of esterifying the racemic chromancarboxylic acid in an organic solvent comprising an alcohol which is in the organic solvent from 1-10% by weight, in the presence of an immobilized lipase derived from a specified microorganism, with the chromancarboxylic being selected from the group consisting of chroman-2-carboxylic

acid, 6-hydroxy-2, 7,8-trimethy-2-carboxymethylchroman, 6-hydroxy-2,7,8-trimethylchroman-2-ylpropionic acid and 6-hydroxy-2-5-7-8 tetramethyl chroman-2-carboxylic acid, to form an ester of an enantiomer of the racemic chromancarboxylic acid which is the optically active chromancarboxylate. See claim 1.

In addition, it is respectfully submitted that the teachings of these applied references would have neither disclosed nor would have suggested such a method as in the present claims, having features as set forth in claim 1, and, moreover, wherein the method further includes a step of separating the remaining chromancarboxylic acid after the esterifying step (that is, separating the mirror image of the chromancarboxylic acid which has been converted into the optically active chromancarboxylate), from a reaction production solution after the esterification. See claim 11; note also claim 18.

In addition, it is respectfully submitted that the teaching of these applied references would have neither disclosed nor would have suggested such method as in the present claims, having features as described in claim 1, and, moreover, wherein the method additionally includes a step of hydrolyzing the optically active chromancarboxylate. See claim 12; note also claim 19.

Furthermore, it is respectfully submitted that the teachings of these applied references would have neither disclosed nor would have suggested such a method for producing an optically active chromancarboxylate, as in the present claims, having features as discussed previously in connection with claim 1, and, additionally, wherein the alcohol is selected from the group of alcohols set forth in claim 6, more specifically, is methanol as set in claim 7; and/or wherein the chromancarboxylic acid is 6-hydroxy 2,5,7, 8-tetramethyl chroman-2-carboxylic acid (see claim 10; note also claim 17)) and/or wherein only one enantiomer of the racemic chromancarboxylic acid is esterified in the step of esterifying (see claim 13); and/or wherein the

immobilized lipase is a biocatalyst which is capable of enantiospecifically esterifying only one enantiomer of the racemic chromancarboxylic acid in the organic solvent comprising the alcohol (see claim 14); and/or wherein the step of separating the mirror image of the chromancarboxylic acid includes adding sodium carbonate to remaining chromancarboxylic acid after the esterifying step, to form a sodium salt of the remaining chromancarboxylic acid, with the sodium salt of the remaining chromancarboxylic acid being transferred into an aqueous layer (see claim 15); and/or wherein during the step of esterifying, water is removed as set forth in claim 16.

The present invention is directed to a method for producing optically active chromancarboxylates, which are useful as raw materials for medicines, agricultural chemicals, chiral building blocks and other functional chemical products, and, for example, usable as intermediates for the production of optically active vitamin E derivates and anti-inflammatory agents.

As described in the last full paragraph on page 1 of Applicants' specification, there have been proposed methods for producing optically active chromancarboxylic acids, including an enantiospecific hydrolysis of (±)-6-hydroxy-2, 5, 7, 8-tetramethylchromancarboxylate using an enzyme catalyst. However, these methods have various problems, including, in the aforementioned enantiospecific hydrolysis, the requirement of complicated procedures for the isolation and purification of the product after the enantiospecific hydrolysis, and for the removal of the enzyme. Accordingly, it is still desired to provide optically active chromancarboxylates by a procedure advantageous for industrial production.

Against this background, and as a result of extensive studies, the present inventors have found that reaction of, e.g., racemic chromancarboxylic acid with, e.g., methanol in an organic solvent in the presence of a biocatalyst allows one of R-

and S-isomers of the racemic mixture to be enantiospecifically and rapidly esterified, and that such a reaction facilitates separation and recovery of the product and can be used as a simple industrial process. Note, e.g., the paragraph bridging pages 2 and 3 of Applicants' specification.

Moreover, Applicants have further found that not only can such optically active chromancarboxylate be efficiently and simply produced, a remaining chromancarboxylic acid not esterified in the esterification step (that is, a mirror image of the chromancarboxylic acid esterified) can also be treated, and the optically active ester and the mirror image easily separated from each other and recovered by simple procedures. In addition, the enzyme catalyst can be repeatedly used.

By conducting the esterification under reduced amounts of water, as in the present invention, in particular, by removing water out of the reaction system, a reduction in reaction rate due to the presence of a large amount of water can be avoided. Note the paragraph bridging pages 8 and 9 of Applicants' specification.

By utilizing an immobilized lipase, a good result in prevention of interfusion of water is achieved. This is confirmed in comparing Examples 2 and 9 of the above-identified application, respectively, on pages 11-13 of Applicants' specification. In Example 2, using an immobilized enzyme, the yield was 10 mol %, while in Example 9, using a non-immobilized enzyme the yield was 6%.

No. 2003-144190 discloses 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, useful as an intermediate for industrial chemicals, agrochemicals, etc., manufactured by asymetrical hydrolysis of mixtures of C1-4 lower alkyl esters of (R)-and (S)- isomers with *Candida* antarctica or lipase from C. antarctica. This patent document discloses that the methyl ester was hydrolyzed with Novozym 435 (immobilized lipase) in a diisopropyl ether-H_2O mixture.

Initially, it is noted that No. 2003-144190 discloses a method of forming the cited chromancarboxylic acid; it is respectfully submitted that this reference does not disclose, nor would have suggested, a method for producing an optically active chromancarboxylate, including the esterification step of the present claims, of a racemic chromancarboxylic acid in an organic solvent comprising an alcohol in the organic solvent from 1-10% by weight, and with a water content of at most 0.5% by weight, and advantages thereof; and/or other features of the present invention as discussed previously and advantages thereof.

It is respectfully submitted that the teachings of Kirchner, et al. would not have rectified deficiencies of No. 2003-144190, such that the presently claimed invention as a whole would have been obvious to one of ordinary skill in the art.

Kirchner, et al. discloses that the authors have recently discovered that porcine pancreatic and yeast lipases can vigorously function and catalyze numerous reactions even in nearly anhydrous organic solvents; and in the present publication, the authors report that in such media the lipases can be used for facile, preparative and efficient resolution of racemates of organic compounds. Note the third paragraph in the left-hand column on page 7072 of this article. This publication goes on to describe, in the last full paragraph in the left-hand column on pages 7072, that when the concentration (activity) of water is decreased, the position of the thermodynamic equilibrium in (lipase-catalyzed) hydrolysis shifts in favor of the esters; and in nearly anhydrous organic media, the hydrolysis reactions (e.g., catalyzed by porcine pancreatic or yeast lipases) are nearly completely reversed, it being found that not only did *Candida* cylindracea lipase almost quantitatively convert a carboxylic acid and an alcohol to the ester in organic solvents, but, when a chiral acid was used, it did so in a highly stereoselective manner. See also the conclusion in the paragraph bridging the left- and right-hand columns on page 7075,

that the two different lipases in the study reported in this article can act as highly stereoselective, practical catalysts in nearly anhydrous organic solvents; and that under such "unnatural" conditions, the enzymes can asymmetrically catalyze reactions of ester and transesterification which are not feasible in aqueous solutions because of the domination of hydrolysis. As a result, a number of optically active alcohols, carboxylic acids, and esters have been prepared on a gram scale. This conclusion goes on to state that there is no need to immobilize enzymes to make the enzymes reusable, because they are insoluble in organic solvents and therefore, can be easily recovered by filtration and used repeatedly.

Thus, note that Kirchner, et al. discloses that there is no need to immobilize enzymes. Taking the teachings of this reference as a whole, even together with the teachings of No. 2003-144190, it is respectfully submitted that the combined teachings of these references would have neither disclosed or would have suggested use of an immobilized lipase which is derived from microorganisms belonging to the genus *Candida*, as in the present claims and the advantages thereof. Moreover, it is respectfully submitted that the combined teachings of these references would have neither disclosed nor would have suggested such method as in the present claims, wherein amount of alcohol in the organic solvent is 1 to 10% by weight, and/or wherein a water content of the organic solvent is at most 0.5% by weight, and advantages thereof.

Interpretation by the Examiner of the teachings of No. 2003-144190, in the paragraph bridging pages 4 and 5 of the Office Action mailed June 25, 2008, is noted. However, it is emphasized that No. 2003-144190 describes asymmetric hydrolysis of mixtures of esters, as indicated by the Examiner in the paragraph bridging pages 4 and 5 of the Office Action mailed June 25, 2008. It is respectfully submitted that such disclosure does not teach, nor would have suggested, the

method of producing optically active chromancarboxylates, including the esterification step, as in the present claims, and the advantages thereof.

In view of the foregoing comments and amendments, reconsideration and allowance of all claims presently pending in the above-identified application are respectfully requested.

To the extent necessary, Applicants hereby petition for an extension of time under 37 CFR 1.136. Kindly charge any shortage of fees due in connection with the filing of this paper, including any extension of time fees, to the Deposit Account of Antonelli, Terry, Stout & Kraus, LLP, Account No. 01-2135 (case 396.45660X00), and please credit any overpayments to such Deposit Account.

Respectfully submitted,

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